Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

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Mycobacterium tuberculosis Infection and Disease (Last updated May 7, 2013; last reviewed May 7, 2013)

Epidemiology

Tuberculosis (TB) infection occurs when a susceptible person inhales droplet nuclei containing *Mycobacterium tuberculosis* organisms. The immune response usually limits multiplication of tubercle bacilli within 2 to 12 weeks after infection. However, viable bacilli persist for years, a condition referred to as latent TB infection (LTBI). Individuals with LTBI are asymptomatic and are not infectious. TB disease (clinically active disease, often with positive cultures) can develop soon after exposure (primary disease) or after reactivation of latent infection.

In individuals with LTBI, the risk of reactivation with TB disease increases very soon after HIV infection.[1] The estimated annual risk of reactivation with TB disease among those with untreated HIV infection and LTBI is 3% to 16% and approximates the lifetime risk for HIV-uninfected individuals with LTBI (~5%).[2] TB disease can occur at any CD4 T lymphocyte (CD4 cell) count, although the risk increases with progressive immunodeficiency.[3]

Antiretroviral therapy (ART) results in a prompt and marked decrease in the incidence of TB disease, an effect that has been documented in settings with low[4] and high case rates.[5,6] Even with the beneficial effects of ART, HIV-infected patients remain at higher risk of TB disease than the general population.[7]

Rates of TB in the United States are declining, with 3.6 new cases per 100,000 population reported in 2010[8] (a total of 11,182 cases). The prevalence of LTBI in the general population of the United States is 4%.[9] The incidence of HIV-related TB has declined more rapidly than the rate of active TB in the general population,[10] which is probably related to the widespread use of ART. In recent years there have been fewer than 1000 new cases of HIV/TB co-infection identified per year in the United States.[8,11,12]

As with TB in the general U.S. population, HIV-related TB disease is increasingly seen in people born outside of the United States.[10] Notably, TB disease has not decreased significantly in recent years among foreign-born persons with HIV disease in the United States.[10,13]

Despite these favorable epidemiological trends, TB remains an important opportunistic illness in the United States. In the era of potent ART, TB disease remained the second most common initial opportunistic illness in New York City.[14] Unlike most opportunistic infections (OIs), TB is transmissible, particularly to others who are HIV-infected. Therefore, clinicians caring for patients with HIV must remain vigilant in efforts to prevent TB, knowledgeable about the clinical presentation of HIV-related TB, and cognizant of the complexities of cotreatment of HIV and TB.

Preventing Exposure

The most common predisposing factor for TB is birth or residence outside of the United States. Therefore, patients with HIV infection who travel or work internationally in settings with a high prevalence of TB should be counseled about the risk of TB acquisition and the advisability of testing for LTBI upon return **(AIII)**. Although some health care and correctional settings in the United States present risks of TB exposure, HIV-infected individuals need to take no precautions beyond those recommended for anyone in those environments **(AIII)**.

Preventing Disease–Diagnosis and Treatment of Latent TB Infection

The estimated annual risk of active TB among HIV-infected patients with LTBI is 3 to 12 times higher than for the general population.[15,16] Furthermore, development of HIV-related TB increases viral load[17] and the risk of HIV disease progression[17] and death[18] compared with CD4-matched, HIV seropositive controls.

Among HIV-infected individuals, treatment of LTBI decreases the risk of TB disease by 62% and the risk of death by 26%.[19] Therefore, prevention of TB disease by screening for and appropriately treating LTBI is a key component of HIV care.

Diagnosis of Latent Tuberculosis Infection

Testing for LTBI at the time of HIV diagnosis should be routine, regardless of an individual's epidemiological risk of TB exposure. Individuals with negative diagnostic tests for LTBI who have advanced HIV infection (CD4 cell count <200 cells/mm^3) and no indications for initiating empiric LTBI treatment should be retested for LTBI once they start ART and attain a CD4 count ≥200 cells/mm^3.[20,21] Annual testing for LTBI is recommended only for HIV-infected patients who are at high risk of repeated or ongoing exposure to those with active TB.

Traditionally, LTBI has been defined by the presence of a positive tuberculin skin test (TST) (≥5 mm of induration at 48–72 hours) in individuals with no clinical or radiographic evidence of TB disease. Although experience with the TST in HIV-infected individuals is extensive, it has several disadvantages: the requirement for two visits to place and read the test, decreased specificity in those who received Bacillus Calmette-Guerin (BCG) vaccination, and decreased sensitivity in those with advanced immunodeficiency.[22] Limitations of the TST have led to interest in interferon-gamma release assays (IGRAs) for detection of LTBI.

Current evidence suggests that IGRAs have higher specificity (92%–97%) than TST (56%–95%), better correlation with surrogate measures of exposure to *M. tuberculosis*,[23] and less cross reactivity because of BCG vaccination or other non-tuberculous mycobacteria exposure.[24,25] Three IGRAs are Food and Drug Administration (FDA) approved and available in the United States. Progressive immunodeficiency is associated with decreased sensitivity of IGRAs, although immunodeficiency may have less impact on the sensitivity of IGRAs than on the sensitivity of TST.[26]

In HIV-infected patients, the correlation between TST and IGRAs is poor to moderate.[27,28] In prospective studies, positive results with either TST or IGRA were associated with an increased risk of developing TB disease;[29,30] in some studies, patients with a positive IGRA were at a higher risk of subsequently developing TB disease than were those with a positive TST.[31,32] For all of its limitations, TST response remains strongly predictive of response to isoniazid preventive therapy among those with HIV infection.[19] Whether the same is true of the IGRAs remains to be demonstrated.

In programmatic settings in the United States, TB screening based on the TST has been suboptimal, with only 47% to 65% of patients completing screening.[33-35] A higher proportion of patients may complete screening for TB if testing is done with IGRAs.

No definitive comparisons have been done of TST and IGRAs for screening HIV-infected individuals in low-burden settings such as the United States. Both TST and the FDA-approved IGRAs are appropriate for TB screening in HIV-infected individuals.[36] Some experts have suggested using both TST and IGRA to screen for LTBI, but the predictive value of this approach is unclear, and it would be more expensive and more difficult to implement. Routine use of both TST and IGRAs to screen for LTBI **is not recommended** in the United States.[36]

Patients with TB disease often demonstrate immune reactivity against *M. tuberculosis* in TST and IGRA testing. Therefore, any positive result with TST or IGRA should trigger expeditious evaluation for the possibility of active TB. Most, but not all, HIV-infected individuals with TB disease have symptoms; the absence of any symptoms has a 97% negative predictive value for culture-positive TB.[37] The addition of a chest radiograph improves the sensitivity of symptom screening algorithms. Sputum culture is the gold standard for diagnosing pulmonary TB disease but is not cost effective for screening HIV-infected patients who are asymptomatic, particularly in the United States, where TB prevalence is very low. Therefore, screening for symptoms (asking for cough of *any* duration) coupled with chest radiography is recommended to exclude TB disease in a patient with a positive TST or IGRA.

When to Start Primary Prophylaxis (i.e., Treating Latent Tuberculosis Infection)

HIV-infected individuals who test positive for LTBI but have no evidence of TB disease should receive LTBI treatment **(AI)**. HIV-infected close contacts of anyone who has infectious TB also should receive prophylaxis, regardless of results of screening tests for LTBI **(AII)**. Notably, for HIV-infected individuals who are anergic and have not had recent contact with anyone with infectious TB, treatment of LTBI is not associated with clinical benefit and **is not recommended (AI)**.[38-41]

Preferred and Alternative Drugs for Treatment of Latent Tuberculosis Infection

Isoniazid administered for 9 months remains the preferred therapy, with proven efficacy, good tolerability, and infrequent severe toxicity **(AII)**. Isoniazid can potentiate the risk of peripheral neuropathy when used with some antiretroviral (ARV) drugs, most notably the dideoxynucleosides (didanosine, stavudine), which are seldom used in clinical practice in the United States. Isoniazid, when used with efavirenz- or nevirapine-based regimens, does not significantly increase risk of hepatitis—the most important adverse effect.[42,43] Isoniazid should be supplemented with pyridoxine at a dose of 25 mg/day to prevent peripheral neuropathy **(AIII)**. A significant disadvantage of the 9-month regimen is that most patients in the United States and Canada do not complete all 9 months of therapy.[44-46] Shorter regimens are more likely to be completed.[44-46] Recent data from an open-label, randomized non-inferiority trial comparing a 3-month regimen of isoniazid plus rifapentine, given by directly observed therapy (DOT) once weekly, with a 9-month regimen of self-administered once daily isoniazid demonstrated that, after 33 months of follow-up, the 3-month isoniazid-rifapentine regimen was as effective as the 9-month isoniazid regimen.[47] The shorter course regimen had the advantage of a higher completion rate. These results led to a recent Centers for Disease Control and Prevention (CDC) recommendation that 3-months of once weekly isoniazid-rifapentine given by DOT can be used as an equal alternative to the standard 9-month regimen.[48] However, the 3-month regimen **is not recommended** for HIV-infected patients receiving ART because of potentially significant drug interactions between rifapentine and some ARV drugs **(AIII)**.[48] Other alternative therapies for chemoprophylaxis are shown in Table 1; the regimen of 2 months rifampin plus pyrazinamide **is not recommended** because of the risk of severe and sometimes fatal hepatotoxicity **(AII)**. Rifampin- or rifabutin-containing regimens may require dose adjustments of ARV or rifabutin (Table 5).

LTBI treatment and ART act independently to decrease the risk of TB disease.[49-51] Therefore, use of both interventions is recommended for those who have LTBI and an indication for ART **(AII)**.

Monitoring of Response to Treatment of Latent Tuberculosis Infection

Patients receiving daily LTBI treatment through self-administration should be seen by the prescribing clinician on a monthly basis to assess adherence and evaluate for possible drug toxicity; generally, not more than 1 month's supply of drugs should be prescribed. Individuals taking a twice-weekly regimen should receive LTBI treatment by direct observation. Risk of hepatitis from isoniazid prophylaxis may not be higher in HIV-infected individuals than those who are uninfected, but baseline measurements of serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin are recommended, and if results are abnormal, testing should be repeated.[52] Individuals with concomitant chronic viral hepatitis may be at increased risk of isoniazid-related hepatotoxicity, and they should be treated for LTBI and closely monitored. With isoniazid, liver enzymes typically increase in the first 3 months but then (through the process of hepatic adaptation) return to normal despite continued therapy. LTBI treatment should be stopped in asymptomatic patients who have a more-than-fivefold increase in AST levels above the upper limit of normal (ULN), symptomatic patients who have a more-than-threefold increase above ULN in AST levels, and patients regardless of symptoms with baseline abnormal transaminases who have a more-than-twofold increase above their baseline AST levels. Patients should be reminded at each visit about potential adverse effects (i.e., unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of the hands and feet, persistent fatigue, weakness or fever lasting 3 days or more, abdominal tenderness, easy bruising or bleeding, and arthralgia) and told to immediately stop isoniazid and return to the clinic for an assessment.

The ultimate decision regarding resumption of therapy with the same or a different agent for LTBI treatment should be made after weighing the risk of additional hepatic injury against the benefit of preventing progression to TB disease[52] and in consultation with an expert in treating LTBI.

Clinical Manifestations of Tuberculosis Disease

Common clinical symptoms of TB disease include productive cough, fever, sweats, weight loss, and fatigue. Culture-positive TB disease can be sub-clinical or oligo-symptomatic.[37] After initiation of ART, immune reconstitution can unmask subclinical active TB, resulting in pronounced inflammatory reactions at the sites of infection.

In HIV-infected individuals, the presentation of active TB disease is influenced by the degree of immunodeficiency.[53,54] In HIV-infected patients without pronounced immunodeficiency, (that is, CD4 cell counts >350 cells/mm^3), HIV-related TB clinically resembles the disease seen in HIV-uninfected patients. Most patients have disease limited to the lungs, and common chest radiographic manifestations include upper lobe fibronodular infiltrates with or without cavitation.[55] Extrapulmonary disease is more common in HIV-infected individuals than in those who are uninfected, regardless of CD4 cell counts, although clinical manifestations are not substantially different from those described in HIV-uninfected individuals. TB must be considered in disease processes involving any site in the body,[56] but especially those related to central nervous system (CNS) or meningeal symptoms in which early TB treatment is essential to improve outcomes.[57,58]

In patients with advanced HIV disease, the chest radiographic findings of pulmonary TB are markedly different than those in patients with less severe immunosuppression. Lower lobe, middle lobe, interstitial, and miliary infiltrates are common and cavitation is less common.[53,55,59] Intrathoracic lymphadenopathy is common, with mediastinal involvement seen more often than hilar adenopathy. Even with normal chest radiographs, patients with HIV infection and pulmonary TB may test positive on acid-fast bacilli (AFB) sputum smears and cultures, particularly if they have cervical node involvement.

The greater the degree of immunodeficiency, the higher the likelihood of extrapulmonary TB, such as lymphadenitis; pleuritis; pericarditis; and meningitis, all with or without pulmonary involvement, and it is found in most TB patients with CD4 cell counts <200 cells/mm^3.[54] In these individuals, TB can be a severe systemic disease with high fevers, rapid progression, and sepsis syndrome.[60]

Histopathologic findings also are affected by the degree of immunodeficiency. Patients with relatively intact immune function have typical granulomatous inflammation associated with TB disease. With progressive immunodeficiency, granulomas become poorly formed or may be completely absent.[54]

Diagnosis of Tuberculosis Disease

Initial diagnostic testing is directed at the anatomic site of symptoms or signs, such as the lungs, lymph nodes, and cerebrospinal fluid (CSF). Even in the absence of pulmonary symptoms or signs, the initial evaluation of a patient suspected of having HIV-related TB should always include a chest radiograph; pulmonary involvement is common whatever the CD4 cell count.[37,61] However, chest radiography is an imperfect screen for sputum culture-positive TB, particularly in patients with advanced immunodeficiency. Therefore, sputum smear and culture should be considered in symptomatic patients with normal chest radiographs who are being evaluated for possible TB disease.

Sputum smear-negative TB is common in HIV-infected patients, particularly those with advanced immunodeficiency and noncavitary disease.[62] However, the yield of sputum mycobacterial culture is not affected by HIV or the degree of immunodeficiency. If a sensitive broth culture technique is used, the sensitivity of sputum culture is quite high. Smear and culture of three sputum specimens is recommended, in that there was a 10% incremental yield for broth culture between the second and third specimens in a recent large study of patients with HIV.[63]

Nodal involvement is common in HIV-related TB, and the combined yield of histopathology, smear, and culture from needle aspirates of enlarged lymph nodes is quite high.[64] Pleural fluid, pericardial fluid, ascites, and CSF should be sampled if there is clinical evidence of involvement. The yield of mycobacterial urine and blood cultures depends upon the clinical setting; in patients with advanced immunodeficiency, the yield of culture from these two readily available body fluids can be relatively high[54,56] and may allow definitive diagnosis and a source for an isolate for drug-susceptibility testing.

Nucleic-acid amplification (NAA) tests provide rapid diagnosis of TB, in contrast to the prolonged time needed for detection of mycobacterial growth, and can be considered for patients with advanced immunodeficiency who are at risk of rapid clinical progression of TB (some assays also provide rapid detection of drug resistance as discussed below). NAA tests have at least two uses in patients with suspected HIV-related TB. First, they are highly predictive of TB in specimens that are AFB smear-positive. Non-tuberculous mycobacterial infections are relatively common in patients with advanced immunodeficiency, and NAA tests can be used to direct therapy and make decisions about the need for respiratory isolation in patients with a smear-positive specimen. Second, NAA tests are more sensitive than AFB smear, producing positive results for 50% to 80% of smear-negative, culture-positive specimens.[65,66] Therefore, the use of a NAA test is recommended on at least one specimen from all patients being evaluated for suspected pulmonary TB.[67] The NAA tests currently available are licensed only for evaluation of sputum samples; much less experience exists with samples from extrapulmonary sites.

Immunological screening for TB with TST and IGRA may be helpful in unusual circumstances that make it difficult to obtain definitive culture evidence for active TB; evidence of prior infection increases the likelihood that a clinical illness may be TB. A negative test, however, should never be interpreted as ruling out TB disease.

Drug-susceptibility testing should be performed on the initial isolates from all patients suspected of having TB because resistance to isoniazid and/or rifampin is associated with an increased risk of treatment failure, recurrent TB, and amplification of resistance to additional TB medications.[68] The presence of multidrug-resistant TB (MDR TB; defined as resistance to at least isoniazid and rifampin) or extensively drug-resistant TB (XDR TB; defined as MDR TB with additional resistance to a fluoroquinolone and either kanamycin, amikacin, or capreomycin) is associated with a markedly increased risk of death.[69] Thus, early identification of drug resistance, with appropriate adjustment of therapy based on results, is critical to successfully treating TB disease and to curbing transmission of drug-resistant *M. tuberculosis*.

Drug-susceptibility testing to first-line TB drugs (i.e., isoniazid, rifampin, ethambutol, and pyrazinamide) should be performed on all patients with TB disease, regardless of the source of the specimen. These tests should be repeated if sputum cultures remain positive for *M. tuberculosis* at or after 4 months of treatment or become positive 1 month or longer after culture conversion to negative. Drug susceptibility testing for second-line TB medications (e.g., fluoroquinolones, aminoglycosides, capreomycin, ethionamide) should be performed only in reference laboratories that have substantial experience with these techniques and should be limited to specimens with resistance to first-line TB medications.

Conventional drug-susceptibility testing is widely used and has been well validated for first-line drugs. The disadvantage of this technique, however, is the combined turnaround time for culture and drug-susceptibility testing, which can be as long as 6 weeks[70] because of the slow growth of *M. tuberculosis* in culture. During this time, patients with drug-resistant TB may be receiving ineffective, empiric first-line TB therapy, which could allow for ongoing transmission, further clinical deterioration, and death—particularly in HIV-infected individuals.[69]

Genotypic testing, which identifies drug-resistance mutations, allows rapid detection of resistance. The relationship between these mutations and drug resistance has been studied for a number of TB medications,[71] and commercial tests have been developed and validated to identify genotypic resistance for rifampin[65,72] and isoniazid.[72] Development is under way of commercial tests to identify genotypic resistance to other TB

medications.[73] Genotypic assays can provide a result in 24 hours and can be performed directly on sputum specimens.

Clinicians who suspect that an HIV-infected patient has drug-resistant TB should make every effort to expedite diagnosis. In the United States, the CDC Division of TB Elimination has a Molecular Detection of Drug Resistance service to make rapid molecular testing for first-and second-line TB medications available for patients who have or are suspected to have TB and do not have local access to such testing (http://www.cdc.gov/tb/topic/laboratory/default.htm).

Drug resistance should be considered in any patient with:

- known exposure to an individual with drug-resistant TB
- residence in a setting with high rates of primary drug-resistant TB, such as a country or area with high rates of drug-resistant TB in newly diagnosed patients[74]
- persistently positive smear or culture results at or after 4 months of treatment
- previous TB treatment, particularly if it was not directly observed or was interrupted for any reason.

Treating Disease

In some settings in the United States, non-tuberculous mycobacterial infections are more common than TB among HIV-infected patients. However, because TB is highly virulent and represents a greater risk of transmission to others, treatment for it is more urgent than for non-tuberculous mycobacterial infections. Furthermore, first-line TB drugs are highly active against *Mycobacterium kansasii*, a relatively common non-tuberculous mycobacterial infection that presents clinically and radiographically like TB.[75] Finally, with appropriate access to broth culture and molecular diagnostics (NAA and genotypic tests for resistance), the time between finding a smear-positive specimen and identifying the species should be short.

TB in individuals with advanced immunodeficiency can be rapidly progressive and fatal if treatment is delayed. Furthermore, such patients often have smear-negative sputum specimens. Therefore, after collection of available specimens for culture and molecular diagnostic tests, empiric treatment for TB is warranted in patients with clinical and radiographic presentation suggestive of HIV-related TB **(AIII)**.

Treatment of suspected TB in HIV-infected individuals is the same as for those who are HIV uninfected and should include an initial four-drug combination of isoniazid, rifampin, pyrazinamide, and ethambutol **(AI)**. An expanded initial regimen—including at least moxifloxacin or levofloxacin and an aminoglycoside or capreomycin—should be used if there is a significant concern about resistance to rifampin, with or without resistance to other drugs **(BIII)**. A TB expert should be consulted if drug resistance is suspected. DOT is recommended for all patients with suspected HIV-related TB **(AII)**. The likelihood of treatment success is further enhanced with comprehensive case management, assistance with housing and other social support, and assistance in establishing or re-engaging with HIV care, if needed (i.e., enhanced DOT).

Drug-susceptible TB is treated with a 2-month intensive phase of the 4 drugs previously listed. Ethambutol can be discontinued when susceptibility to isoniazid and rifampin has been confirmed. Pyrazinamide may be discontinued after 2 months. Thereafter, isoniazid and a rifamycin are used in the continuation phase of therapy.

Intermittent dosing (administration less often than daily) of anti-TB treatment facilitates DOT. However, regimens that included twice- or thrice-weekly dosing during the intensive phase have been associated with an increased risk of treatment failure or relapse with acquired drug resistance to the rifamycin class.[76-78] Therefore, daily therapy (5–7 days per week) given as DOT is recommended during the intensive phase **(AII)**.

Daily (5–7 days per week) or thrice-weekly dosing is recommended during the continuation phase of therapy **(AII)**. Regimens that included once- or twice-weekly dosing during the continuation phase of therapy were

associated with increased risk of treatment failure or relapse with acquired rifamycin resistance.[79,80] Whether there is a difference between daily and thrice-weekly dosing during the continuation phase of therapy has not been adequately studied in randomized trials; in observational studies and a meta-analysis, thrice-weekly therapy during the continuation phase was not associated with an increased risk of adverse TB outcomes (i.e., treatment failure, recurrence, or acquired drug resistance).[81]

The optimal duration of TB treatment for patients with HIV infection and drug-susceptible TB disease is unknown. In general, the outcomes have been good with 6-month regimens (2 months of isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampin) given as DOT to patients with HIV co-infection. A randomized trial in the United States showed excellent and comparable outcomes of TB therapy among patients assigned to 6 months or 9 months of therapy, but the trial was underpowered.[82] Two trials in high-burden settings showed higher risks of recurrent TB among patients treated with 6 months of therapy compared with those assigned to 9-[76] or 12-month regimens.[83] However, the applicability of these two trials is uncertain in low-burden settings in which ART is used, such as the United States.

Pending the outcome of further studies, 6 months of therapy for most patients with HIV-related, drug-susceptible TB disease is recommended **(BII)**. Extension of therapy to 9 months is recommended for those with a positive 2-month sputum culture **(BII)**. Extension of therapy to 9 to 12 months is also recommended for patients with CNS involvement **(BII)**. Treatment for 6 to 9 months is recommended for patients with bone and joint TB **(BII)**. The duration of therapy should be based on number of doses received, not on calendar time **(BIII)** because there may be substantial differences between dose number and calendar time if doses were missed due to poor adherence or for management of problems with tolerability or toxicity.

Adjunctive corticosteroid therapy increases survival for patients with HIV-related TB involving the CNS[84] and pericardium[85] **(AI)**. No trials to date have compared different doses and treatment durations of adjunctive corticosteroids. Dexamethasone was used in trials of adjunctive corticosteroids for CNS disease (0.3–0.4 mg/kg/day for 2–4 weeks, then taper 0.1 mg/kg per week until dose of 0.1 mg/kg, then 4 mg per day and taper by 1 mg/week; total duration of 12 weeks); prednisone or prednisolone was used in trials of pericardial disease (60 g/day and taper 10 mg per week; total duration of 6 weeks).

Special Considerations with Regard to Starting ART

Optimal management of HIV-related TB requires that both infections be addressed; sequential treatment of TB followed by HIV treatment **is not recommended**.[86] Co-treatment of HIV and TB is complex because of the adherence demands of multidrug therapy for two infections, drug-drug interactions between the rifamycins and many ARV drugs, overlapping side effect profiles of antituberculosis and ARV drugs, and the frequency of immune reconstitution inflammatory syndrome (IRIS). Despite these substantial clinical challenges, co-treatment of HIV-related TB improves survival,[86] particularly in patients with CD4 counts <50 cells/mm^3; decreases the risk of additional opportunistic illnesses including TB;[87] can achieve high rates of viral suppression;[88] and may improve TB treatment outcomes.[89]

Starting ART early in the course of TB treatment can complicate clinical management because of increased pill burden, drug toxicities, drug interactions, and IRIS events. However, recently completed randomized clinical trials demonstrate that ART can be safely given during TB treatment without jeopardizing HIV treatment responses and that ART reduces mortality and HIV-related illnesses.[86-88]

The SAPIT trial randomized 642 South African adults with CD4 cell counts <500/mm^3 and AFB smear-positive TB to start ART according to one of three strategies; at TB treatment initiation; after the intensive phase of TB therapy but before TB treatment completion; or after TB treatment completion.[86] The study was stopped early when the mortality of the 2 integrated treatment arms was 56% lower than the sequential treatment arm, demonstrating that ART should be started before completion of TB treatment. Notably, there was a survival benefit across the range of CD4 cell counts among patients enrolled, including within the stratum of baseline CD4 counts from 200 to 500 cells/mm^3. Updated results of the SAPIT trial indicated that the benefit of early ART was greatest for those with CD4 counts of <50 cells/mm^3 and that individuals with

higher CD4 cell counts who started ART within the first 4 weeks of the continuation phase of TB treatment had a lower incidence of IRIS and adverse events.[90]

The CAMELIA and A5221 trials shed further light on the optimal timing of ART during the course of TB treatment. In CAMELIA, 661 adults in Cambodia with confirmed pulmonary TB and a median CD4 count of 25 cells/mm^3 (interquartile range [IQR] 10,56) were randomized to receive ART at 2 or 8 weeks after starting TB treatment. The risk of death was decreased from 27% in the 8-week arm to 18% in the 2-week arm and, among those who survived, viral suppression rates were very high (>95%).[88] The ACTG A5221 study randomized 809 patients from North America, South America, Africa, and Asia with confirmed or suspected TB and a median CD4 count of 77 cells/mm^3 (IQR 33,146) to immediate ART (within 2 weeks) or early ART (8–12 weeks).[87] A new OI or death occurred among 12.9% of patients in the immediate arm and 16.1% in the early arm by week 48 ($P = 0.45$). In patients with screening CD4 counts <50 cells/mm^3, 15.5% of patients on the immediate arm versus 26.6% on early ART experienced AIDS or death, ($P = 0.02$). Tuberculous-associated IRIS (TB-IRIS) was more common in the immediate ART arm (11%) compared with the early arm (5%) ($P = 0.002$). Viral suppression rates were similar between the arms.

Other recently completed smaller and non-randomized studies provide further support for early ART initiation. In the PART study, which included only patients with TB and HIV with CD4 cell counts >350 cells/mm^3, even a short 6-month course of ART started at TB diagnosis resulted in lower rates of AIDS or death compared with delaying ART until a CD4 threshold of 250 cells/mm^3.[91] A recent retrospective analysis of HIV-infected adults with XDR TB showed a 62% reduction in mortality in those who received ART.[92]

The optimal strategy in TB meningitis is less clear. A randomized trial conducted in Vietnam compared ART initiated immediately or 2 months after starting TB treatment in 253 patients with HIV-related TB meningitis.[93] This study did not show a survival benefit for early initiation of ART. On the contrary, early ART was associated with significantly more severe adverse events (102) compared with the deferred ART arm (87; $P = 0.04$). The overall mortality rates and severe adverse event rates in this study were extraordinarily high (58% and 89–90%, respectively), in part reflecting the very ill AIDS population, and may not be generalizable to other settings. Nonetheless, caution in early ART initiation is warranted in patients with tuberculous meningitis.

When TB occurs in patients already on ART, treatment for TB must be started immediately **(AIII)**, and ART should be modified to reduce the risk of drug interactions and maintain virologic suppression. When TB occurs in the setting of virologic failure, ART drug-resistance testing should be performed and a new ART regimen constructed, along with intensified adherence counseling to achieve virologic suppression and minimize drug interactions with the anti-TB regimen.

In summary, ART is recommended in all HIV-infected persons with TB **(AI)**. For ART-naive patients, ART should be started within 2 weeks when the CD4 count is <50 cells/mm^3 and by 8 to 12 weeks for all others **(AI)**. Given the need for the initiation of five to seven new medications in a short time, adherence support should be offered. In patients with TB meningitis and low CD4 cell counts, early ART may pose a risk that calls for careful monitoring and consultation with experts. Early ART initiation requires close collaboration between HIV and TB care clinics, expertise in management of ART regimen selection, and support and adherence services for clients.

Drug-drug interactions in the treatment of HIV-related tuberculosis

The rifamycin class of antibiotics is the key to effective, short-course TB treatment. However, the rifamycins currently available (rifampin, rifabutin, and rifapentine) have clinically significant interactions with a number of ARV drugs (Table 5). These drug-drug interactions are complex, but most result from the potent induction by the rifamycin of genes involved in the metabolism and transport of ARV agents.

The preferred cotreatment regimen for HIV-related TB disease is rifampin-based TB therapy with an ARV regimen of efavirenz plus two nucleoside(tide) analogues **(AII)**. Efavirenz-based ART is associated with

excellent TB and HIV treatment outcomes and has low rates of serious toxicity.[94] Data conflict on the magnitude of the change in efavirenz concentrations when co-administered with rifampin. Early studies reported a 26% reduction in efavirenz exposure,[95] but more recent and larger studies in HIV-infected patients with TB (including patients with higher body weight) have not shown a significant effect of rifampin on efavirenz exposure.[96,97] Previous recommendations to increase the dose of efavirenz, especially in patients who weigh >60 kg, are thus not supported by good data and have several disadvantages; complexity of dosing, inability to take advantage of the simplicity of the co-formulation of efavirenz, tenofovir, and emtricitabine, and possibility of increased neuropsychiatric side effects. Given the excellent treatment outcomes of co-treatment with standard-dose efavirenz,[94,98] the 600-mg daily dose of efavirenz is recommended **(BII)**.

Rifampin has a more significant effect on the concentration of nevirapine, but clinical outcomes have been reasonably good among patients on a co-treatment regimen of rifampin-based TB treatment with an ARV regimen of nevirapine plus two nucleoside analogues.[94,99,100] However, a recent randomized controlled trial showed that a once daily nevirapine regimen used with didanosine and lamivudine was inferior to a once daily efavirenz regimen used with the same NRTIs in HIV-associated TB treated with a rifampin regimen.[101] For patients absolutely unable to take efavirenz due to intolerance or early pregnancy, nevirapine-based ART can be used, but the lead-in dose of nevirapine should be omitted for patients who are established on rifampin for at least 2 weeks and plasma HIV RNA levels should be monitored closely.[94]

For patients who have HIV strains resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) or are unable to tolerate efavirenz and nevirapine, the preferred co-treatment regimen is rifabutin-based TB therapy with an ARV regimen that includes a ritonavir-boosted protease inhibitor (PI) **(BIII)**. The dramatic effects of rifampin on serum concentrations of lopinavir can be overcome by high-dose ritonavir,[102] but high rates of hepatotoxicity have been reported when adjusted ritonavir-boosted PIs were given with rifampin to healthy volunteers.[103-105] Rifabutin has little effect on ritonavir-boosted lopinavir[106] or atazanavir,[107] and its co-administration results in moderate increases in darunavir[108] and fosamprenavir concentrations.[109]

However, all PIs markedly increase serum concentrations of rifabutin (and one of its principal metabolites, desacetyl-rifabutin). Therefore, the dose of rifabutin must be decreased to avoid dose-related toxicity, such as uveitis.[110] The magnitude of the dose reduction for rifabutin remains somewhat controversial. In studies of healthy volunteers, a 150-mg dose every other day together with a ritonavir-boosted PI achieved serum concentrations of rifabutin comparable to or higher (with much higher concentrations of the desacetyl metabolite) than those achieved with 300 mg rifabutin daily in the absence of a PI.[108,109,111] However, among HIV-infected individuals with TB, there have been case reports of acquired rifamycin resistance with 150-mg thrice-weekly dosing in the presence of a boosted PI-based ARV regimen.[112,113]

Pending additional data, we recommend a dosage of 150 mg of rifabutin daily (at least during the first 2 months of TB treatment) for patients who are on a PI-containing ARV regimen **(BIII)**. Therapeutic drug monitoring for rifabutin can be considered in this situation.[113] Close monitoring of adherence to ART is important because these reduced doses of rifabutin would be inadequate if patients stopped taking the PI.

Clinical experience is minimal for use of rifamycins with raltegravir, CCR5 receptor antagonists, and second-generation NNRTIs. Raltegravir concentrations are decreased when coadministered with rifampin, and a raltegravir dose increase (to 800 mg twice daily [BID]) is recommended but has not been evaluated in clinical trials. Similarly, there is no published experience with rifampin or rifabutin and elvitegravir boosted with cobicistat, although the drug interactions and required dose adjustments are expected to be similar to those with boosted PIs. These ARV drugs should be used only when required for ARV potency and in consultation with an expert in this field. As new antiretroviral drugs are approved, recommendations will be developed about their use in conjunction with antituberculous regimens.

The breadth and magnitude of drug-drug interactions between the rifamycins and many ARV drugs can be daunting. Nevertheless, every effort should be made to include a rifamycin in the TB treatment regimen; the

drug-drug interactions between rifamycins and ARV drugs should be managed, not avoided. Rifamycins remain the most potent drug class for TB treatment, and regimens that included just 2 months of rifampin were associated with increased risks of treatment failure and recurrence among patients with HIV-related TB.[114,115] Patients with rifamycin-susceptible *M. tuberculosis* isolates should only be treated with a regimen that does not contain a rifamycin if they have had a serious event that is highly likely to be due to the drug.

Monitoring of Response to Therapy and Adverse Events (including IRIS)

Patients with pulmonary TB should have monthly sputum smears and cultures to document culture conversion on therapy (defined as two consecutive negative cultures). Sputum cultures typically convert to negative in patients with susceptible TB within the first 2 months of first-line TB therapy; sputum culture conversion may take longer in patients with a high burden of disease, such as cavitary TB disease.[116] Patients who have not had sputum culture conversion at or after 4 months of therapy should be evaluated for possible treatment failure and acquired drug resistance.

Adverse events during the treatment of HIV-related TB are common.[52,117-120] Because alternative drugs often have less efficacy and more toxicities than first-line anti-TB drugs and diagnosing a drug reaction and determining the responsible agent can be difficult, the first-line drugs (especially isoniazid, rifampin, or rifabutin) should not be stopped permanently without strong evidence that a specific anti-TB drug was the cause of the reaction. In such situations, consultation with a specialist in treating TB disease in HIV-infected individuals is recommended.

Gastrointestinal (GI) reactions are common with many of the anti-TB medications.[121] If GI symptoms occur, AST and bilirubin should be measured to determine if hepatic toxicity is the cause. Typically, GI symptoms not related to hepatic toxicity should be managed without discontinuing TB medications; initial approaches should include either changing the time of administration or administering drugs with food.

Skin rashes are common with all anti-TB drugs. If rash is minor, affects a limited area, or causes pruritus, antihistamines should be administered for symptomatic relief and all anti-TB medications continued. If the rash is severe, all TB medications should be stopped until the rash is substantially improved, and TB drugs restarted one by one at intervals of 2 to 3 days. Rifampin or rifabutin should be restarted first because their role in treatment is critical. If the rash recurs, the last drug that had been added should be stopped. If a petechial rash thought to be caused by thrombocytopenia occurs, rifampin or rifabutin should be stopped permanently.[122] If a generalized rash associated with either fever or mucous membrane involvement occurs, all drugs should be stopped immediately, patients should be switched to alternative anti-TB agents, and LTBI or TB treatment should be managed in consultation with a specialist.

Fever in HIV-infected patients who have been receiving effective TB therapy for several weeks may represent drug fever, another infection, or IRIS.[123] If superinfection or worsening TB is excluded as a potential cause, all TB drugs should be stopped. Once the fever has resolved, the general guidelines described for restarting/stopping drugs in the presence of a rash should be followed.

An increase in AST occurs in approximately 20% of patients treated with the standard four-drug, anti-TB regimen.[124] Drug-induced liver injury can be caused by isoniazid, rifamycins, pyrazinamide, or a number of ARV drugs. Drug-induced liver injury is defined as an AST elevation to ≥3 times the ULN or baseline (whichever is higher) in the presence of symptoms, or >5 times the ULN in the absence of symptoms.[125] In addition to AST elevation, disproportionate increases in bilirubin and alkaline phosphatase occasionally occur. This latter pattern is more consistent with rifamycin hepatotoxicity than with isoniazid or pyrazinamide hepatotoxicity. In most patients, asymptomatic aminotransferase elevations spontaneously resolve.

In the absence of symptoms, elevations of AST <3 times ULN should not prompt changes of TB therapy, but the frequency of clinical and laboratory monitoring should be increased. If AST levels are ≥5 times the ULN regardless of symptoms, >3 times the ULN with symptoms, or if a significant increase in bilirubin and/or alkaline phosphatase occurs, hepatotoxic drugs should be stopped and patients should be evaluated

immediately. For any substantial new transaminase or bilirubin elevation, serologic testing for hepatitis A, B, and C should be performed, and patients should be questioned regarding symptoms suggestive of biliary tract disease and exposures to alcohol and other hepatotoxins.

If anti-TB drugs must be stopped for hepatotoxicity, it may be prudent to substitute more than three nonhepatotoxic anti-TB drugs (depending on the stage of TB therapy, the degree of clinical illness, and the severity of immunodeficiency) until the specific cause of hepatotoxicity can be determined and an alternative longer-term regimen constructed. The anti-TB medications should be restarted one at a time after the AST level returns to <2 times the ULN or to near baseline for patients with pre-existing abnormalities. Because the rifamycins are a critical part of the TB regimen and are less likely to cause hepatotoxicity than isoniazid or pyrazinamide,[45,124] they should be restarted first. If no increase in AST occurs after 1 week, isoniazid may be restarted. Pyrazinamide can be restarted 1 week after isoniazid if AST does not increase. If symptoms recur or AST increases, the last drug added should be stopped. If rifampin and isoniazid are tolerated and hepatitis was severe, pyrazinamide should be presumed responsible and should be discontinued. In this last circumstance, therapy can be extended to 9 months with rifampin and isoniazid alone, depending on the number of doses of pyrazinamide taken, severity of disease, and bacteriological status.

In patients with recently diagnosed or undiagnosed active TB, TB-IRIS is a common early complication. The condition is thought to result from the recovering immune system driving inflammatory reactions directed at *M. tuberculosis* antigen present at sites of disease.[126-128] TB-IRIS is characterized by excessive local or systemic inflammation. Two forms of TB-IRIS are recognized: paradoxical TB-IRIS and unmasking TB-IRIS. Proposed case definitions for these syndromes have been published.[129]

Paradoxical TB-IRIS occurs in patients who are diagnosed with active TB before starting ART. Typically, these patients have had clinical improvement on TB treatment before starting ART. Within the first weeks of ART (though sometimes later) they develop new or recurrent symptoms and new, worsening, or recurrent clinical and radiologic features of TB. Common and important manifestations of paradoxical TB-IRIS include hectic fevers, new or worsening lymphadenopathy, and new or worsening pulmonary infiltrates. Mortality from paradoxical TB-IRIS is uncommon,[127,130] but life-threatening manifestations include enlarging cerebral tuberculomas, meningitis, enlargement of pericardial effusions causing cardiac tamponade, extensive pulmonary involvement with respiratory failure, nodal enlargement causing airway obstruction, and splenic rupture due to rapid enlargement.[127,131,132] In patients with disseminated TB, hepatic TB-IRIS is common and manifests with tender hepatic enlargement, nausea and vomiting, cholestatic liver function derangement, and occasionally jaundice.[133,134] On liver biopsy, a granulomatous hepatitis is demonstrated. Hepatic TB-IRIS may be difficult to differentiate from drug-induced liver injury.

Paradoxical TB-IRIS is relatively common in patients starting ART while on TB treatment (8%–43%). A recent meta-analysis provided a pooled estimate of incidence of IRIS of 15.7%, with a case fatality rate of 3.2%.[130] Onset of paradoxical TB-IRIS symptoms typically occurs 1 to 4 weeks after ART is initiated.[135-140] On average, the syndrome lasts for 2 to 3 months,[131,141] but some patients have symptoms for months and, in rare cases, local manifestations may persist or recur more than a year after onset.[129,141,142]

The most consistently identified risk factors for paradoxical TB-IRIS are low CD4 cell count at start of ART (especially CD4 cell counts <100 cells/mm^3);[133,143] disseminated or extrapulmonary TB;[131,137,139,143] and a short interval between starting TB treatment and ART, particularly within the first 2 months of TB treatment.[131,136,138]

The diagnosis of paradoxical TB-IRIS can be challenging and there is no definitive confirmatory test. Thus, diagnosis relies upon a characteristic clinical presentation: improvement of TB symptoms prior to ART; deterioration with features of TB soon after starting ART; demonstration of a response to ART (CD4 rise and/or viral load reduction); and, most important, investigations to exclude alternative causes for deterioration, particularly undetected TB drug resistance.

Most cases of paradoxical TB-IRIS are self-limiting. Many patients require symptomatic therapy (analgesia, antiemetics) and, if symptoms are significant, anti-inflammatory therapy should be considered. One

randomized, placebo-controlled trial among patients with moderately severe paradoxical IRIS showed that treatment with prednisone (1.5 mg/kg/day for 2 weeks followed by 0.75 mg/kg/day for 2 weeks) resulted in a reduction of a combined endpoint of days hospitalized plus outpatient therapeutic procedures.[144] Those on prednisone experienced more rapid symptom and radiographic improvement. No mortality benefit was demonstrated, but immediately life-threatening cases, such as those with neurological involvement, were excluded from this study. The above study,[144] observational data,[132] and clinical trials of patients treated with corticosteroids at the time of TB meningitis presentation (in which corticosteroids reduced mortality)[84] suggest that corticosteroids should be used for TB-IRIS involving the CNS. For a minority of patients, 4 weeks of prednisone is insufficient, and they may require more gradual tapering of steroids over a few months **(BIII)**.[144] Tapering of corticosteroids should be guided by repeated clinical assessment of symptoms and markers of inflammation, such as fever and tachycardia **(BIII)**. Corticosteroids should be avoided in patients with Kaposi sarcoma[145] and where the diagnosis of paradoxical TB-IRIS is not certain.

Some clinicians use non-steroidal, anti-inflammatory drugs to provide symptomatic relief in patients with mild TB-IRIS **(CIII)**. Needle aspiration of enlarging serous effusions, large tuberculous abscesses, or suppurative lymphadenitis may provide symptomatic relief. Repeated aspirations may be required because collections and effusions often reaccumulate.[131]

Unmasking TB-IRIS can occur in patients who have unrecognized TB at the time they start ART (because it is sub-clinical, is oligo-symptomatic, or the diagnosis has been missed). These patients present with a particularly accelerated and inflammatory presentation of TB in the first weeks of ART.[129] A common presentation is pulmonary TB presenting with rapid symptom onset and clinical features similar to bacterial pneumonia, with high fever, respiratory distress, sepsis syndrome, and consolidation on chest radiograph.[129,146-148] Focal inflammatory manifestations such as abscesses and lymphadenitis also may develop.[149] The treatment is standard TB treatment and corticosteroids if the manifestations are life threatening, although there is no clinical trial evidence to support their use **(BIII)**.

Managing Treatment Failure

The causes of treatment failure include undetected primary drug resistance, inadequate adherence to therapy, prescription of an incorrect or inadequate regimen, subtherapeutic drug levels due to malabsorption or drug interactions, superinfection with drug-resistant *M. tuberculosis*, and acquired drug resistance.

Patients with suspected treatment failure should be evaluated with a history, physical exam, and chest radiograph to determine whether they have clinically responded to therapy, even though their cultures have not converted. The initial culture results and drug-resistance tests, treatment regimen, and adherence also should be reviewed. Samples from all available sites should be taken for repeat culture and drug-susceptibility testing, and strong consideration should be given to performing rapid resistance testing on direct specimens or positive cultures to identify acquired drug resistance or superinfection with a drug-resistant strain.

Pending results of repeat cultures and rapid resistance testing, empiric TB treatment should be broadened using second-line TB drugs, in consultation with an expert in the field **(BIII)**.

Managing drug-resistant tuberculosis

Clinical trials are needed to determine the optimal management of patients with drug-resistant TB. The most active and effective TB drugs are those used in first-line TB treatment regimens (isoniazid and rifampin, in particular). When resistance to these medications develops, alternative combinations of first- and second-line TB medications must be used, but their optimal use has not been tested using rigorous clinical trials.

The standard first-line TB regimen initially was believed to be adequate for isoniazid mono-resistant TB. However, growing evidence demonstrates that there is an increased risk of treatment failure associated with baseline isoniazid resistance,[150] particularly in patients with HIV co-infection.[76] Substitution of a fluoroquinolone (levofloxacin or moxifloxacin) for isoniazid is suggested for at least the first 2 months of

therapy **(BIII)** and perhaps for the continuation phase with rifampin and ethambutol as well **(CIII)**, for a total duration of treatment of 9 months **(BII)**.

The complexity and duration of treatment are substantially increased for TB strains resistant to rifampin alone or to rifampin and other drugs. These patients require treatment with second-line, and perhaps third-line, TB medications that should be selected based on drug-susceptibility testing results, and that are less effective, more toxic, and require 12 to 24 months of treatment.[151] Furthermore, therapy for MDR-TB is rapidly evolving as novel drugs for TB treatment are introduced. Thus, treatment of MDR-TB should involve an expert with experience in treating drug-resistant TB. If a local expert is not available, one option is to contact a CDC Regional Training and Medical Consultation Center at http://www.cdc.gov/tb/education/rtmc/default.htm.

Preventing Recurrence

The risk of recurrent TB in patients with HIV co-infection appears to be somewhat higher than in those who are HIV-uninfected and receiving the same TB treatment regimen in the same setting.[152] In TB-endemic settings, much of the increased risk of recurrent TB appears to be due to the higher risk of re-infection with a new strain of *M. tuberculosis*, with subsequent rapid progression to TB disease.[153,154] In settings with low rates of TB (e.g., the United States), recurrent TB due to re-infection is uncommon, even among HIV-infected patients.[155]

Several interventions have been suggested to decrease the risk of recurrent TB among patients with HIV coinfection: longer TB treatment regimens, more frequent dosing of TB therapy, post-treatment isoniazid therapy, and use of ART. None of these interventions has been adequately evaluated in randomized trials in settings with low TB burdens. Post-treatment isoniazid (6–9 months of daily isoniazid therapy after the completion of standard multidrug therapy) has been shown to be effective in high-burden settings in which the risk of re-exposure is high,[156,157] suggesting that this intervention decreases the risk of re-infection. However, post-treatment isoniazid is not recommended in low-burden settings such as the United States. Given its beneficial effects on the risk of initially developing TB disease, it is very likely that ART decreases the risk of re-infection with TB.

Special Considerations During Pregnancy

HIV-infected pregnant women who do not have documentation of a prior negative TB screening test result or who are at high risk for repeated or ongoing exposure to individuals with active TB should be tested during pregnancy **(AIII)**. The frequency of anergy is not increased during pregnancy, and routine anergy testing for HIV-infected pregnant women is not recommended.[158-161] There are only limited data on the performance of the IGRAs for diagnosis of LTBI in pregnant women. In a study in HIV-infected pregnant women in Kenya, a positive IGRA result was associated with a 4.5-fold increased risk of developing active TB disease; in women with CD4 cell counts <250 cells/μL, a positive IGRA result was associated with a 5-fold increased risk of maternal mortality or active TB and a 3-fold increased risk of either active TB or mortality in infants.[162]

If LTBI is diagnosed during pregnancy and active TB has been ruled out, preventive treatment should be considered during pregnancy **(BIII)**. The potential risk of isoniazid toxicity must be weighed against the consequences of active TB developing during pregnancy and postpartum. Studies in HIV/TB co-infected individuals who are not receiving ART have found a high risk of progression from LTBI to active TB (10% per year) and there is a high risk of maternal and infant mortality in HIV-infected pregnant women with active TB.[163,164] However, the risk of progression from LTBI to active TB in individuals on ART is significantly decreased;[165] therefore, HIV-infected pregnant women should be receiving ART for prevention of mother-to-child transmission. Pregnant women receiving isoniazid should receive daily pyridoxine supplementation as they are at risk of isoniazid-associated peripheral neuropathy.[166]

The diagnostic evaluation for TB disease in pregnant women is the same as for non-pregnant adults. Chest

radiographs with abdominal shielding result in minimal fetal radiation exposure. An increase in pregnancy complications and undesirable outcomes including preterm birth, low birthweight, and intrauterine growth retardation might be observed among pregnant women with either pulmonary or extrapulmonary TB not confined to the lymph nodes, especially when treatment is not begun until late in pregnancy.[158-161,167-170] Congenital TB infection of the infant has been reported, although it appears relatively uncommon.[171] However, in 1 study of 107 women with active TB during pregnancy in South Africa, TB was detected in 16% of neonates (12 by culture and 4 by smear microscopy) sampled within the first 3 weeks of life.[172]

Treatment of TB disease for pregnant women should be the same as for non-pregnant women, but with attention given to the following considerations **(BIII)**:

- Although isoniazid is not teratogenic in animals or humans, hepatotoxicity caused by isoniazid might occur more frequently in pregnancy and the postpartum period.[173] Monthly monitoring of liver transaminases during pregnancy and the postpartum period is recommended **(CIII)**.
- Rifampin is not teratogenic in humans.
- Pyrazinamide is not teratogenic among animals. Experience is limited with use in human pregnancy. Although the World Health Organization and the International Union Against Tuberculosis and Lung Diseases[174,175] have made recommendations for the routine use of pyrazinamide in pregnant women, it has not been recommended for general use during pregnancy in the United States because data characterizing its effects in this setting are limited.[176] If pyrazinamide is not included in the initial treatment regimen, the minimum duration of TB therapy should be 9 months **(CIII)**. The decision regarding whether to include pyrazinamide for treatment should be made after consultation among obstetricians, TB specialists, and patients, taking into account gestational age and likely susceptibility pattern of the infecting strain.
- Ethambutol is teratogenic among rodents and rabbits at doses that are much higher than those used among humans. No evidence of teratogenicity has been observed among humans. Ocular toxicity has been reported among adults taking ethambutol, but changes in visual acuity have not been detected in infants born after exposure *in utero*.

Experience with using the majority of the second-line drugs for TB during pregnancy is limited.[177-180] MDR-TB in pregnancy should be managed in consultation with a specialist. Therapy should not be withheld because of pregnancy **(AIII)**. The following concerns should be considered when selecting second-line anti-TB drugs for use among pregnant women:

- Streptomycin use has been associated with a 10% rate of eighth nerve toxicity in infants exposed *in utero*; its use during pregnancy should be avoided if possible **(AIII)**.
- Hearing loss has been detected in approximately 2% of children exposed to long-term kanamycin therapy *in utero*; like streptomycin, this agent should typically be avoided if possible **(AIII)**. The fetus is at a theoretical risk for ototoxicity with *in utero* exposure to amikacin and capreomycin, but this risk has not been documented and these drugs might be alternatives when an aminoglycoside is required for treatment of MDR-TB **(CIII)**.
- Because arthropathy has been noted in immature animals exposed *in utero* to quinolones, quinolones are typically not recommended for pregnant women and among children aged <18 years **(CIII)**. However, studies evaluating quinolone use in pregnant women did not find an increased risk of birth defects or musculoskeletal abnormalities.[181,182] Thus, fluoroquinolones can be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing **(CIII)**.[183]
- Para-aminosalicylic acid is not teratogenic among rats or rabbits.[176] In one study, a possible increase in limb and ear anomalies was reported among 143 infants delivered by women who were exposed during

the first trimester.[184] No specific pattern of defects and no increase in rate of defects have been detected among subjects in other human studies, indicating that this agent can be used with caution if needed **(CIII)**.

- Ethionamide has been associated with an increased risk for several anomalies among mice, rats, and rabbits after high-dose exposure; no increased risk for defects was noted with doses similar to those used among humans, but experience is limited with use during human pregnancy. Thus, ethionamide should be avoided unless its use is necessary **(CIII)**.
- No data are available from animal studies or reports of cycloserine use in humans during pregnancy.

Recommendations for Treating *Mycobacterium Tuberculosis* Infection and Disease (page 1 of 2)

Treating LTBI (to prevent TB disease)

Indications:

- (+) screening test[a] for LTBI, no evidence of active TB, and no prior history of treatment for active or latent TB **(AI)**;
- Close contact with a person with infectious TB, regardless of screening test result **(AII)**

Preferred Therapy (Duration of Therapy = 9 Months):

- INH 300 mg PO daily + pyridoxine 25 mg PO daily **(AII)** *or*
- INH 900 mg PO BIW (by DOT) + pyridoxine 25 mg PO daily **(BII)**

Alternative Therapies:

- RIF 600 mg PO daily x 4 months **(BIII)** *or*
- RFB (dose adjusted based on concomitant ART) x 4 months **(BIII)**
- For persons exposed to drug-resistant TB, select anti-TB drugs after consultation with experts or with public health authorities **(AII)**

Treating Active TB Disease

- After collecting specimen for culture and molecular diagnostic tests, empiric treatment should be initiated in HIV-infected persons with clinical and radiographic presentation suggestive of HIV-related TB **(AIII)**.
- DOT is recommended for all patients requiring treatment for HIV-related TB **(AII)**.
- Please refer to the table below for TB drug dosing recommendations and to Table 5 for dosing recommendations of ARV drugs when used with RIF or RFB.

For Drug-Sensitive TB

Intensive Phase (2 Months)

- Daily therapy (5–7 days per week) given as DOT is recommended for all patients during the intensive phase **(AII)**.
- INH + (RIF or RFB) + PZA + EMB **(AI)**; if drug susceptibility report shows sensitivity to INH & RIF, then EMB may be discontinued.

Continuation Phase (For Drug Susceptible TB)

- INH + (RIF or RFB) daily (5–7 days per week) or TIW **(AII)**

Total Duration of Therapy:

- Pulmonary, drug-susceptible TB—6 months **(BII)**
- Pulmonary TB & positive culture at 2 months of TB treatment—9 months **(BII)**
- Extrapulmonary TB w/CNS—9 to 12 months **(BII)**
- Extrapulmonary TB w/bone or joint involvement—6 to 9 months **(BII)**
- Extrapulmonary TB in other sites—6 months **(BII)**
- The total duration of therapy should be based on number of doses received, not on calendar time **(BIII)**.

For Drug-Resistant TB

Empiric Therapy for Suspected Resistance to Rifamycin +/- Resistance to Other Drugs:

- INH + (RIF or RFB) + PZA + EMB + (moxifloxacin or levofloxacin) + (an aminoglycoside or capreomycin)

- Therapy should be modified based on drug susceptibility results
- A TB expert should be consulted

Resistant to INH

- (RIF or RFB) + EMB + PZA + (moxifloxacin or levofloxacin) for 2 months **(BII)**; followed by (RIF or RFB) + EMB + (moxifloxacin or levofloxacin) for 7 months **(BII)**

Resistant to Rifamycins +/- Other Antimycobacterial Agents:

- Therapy and duration of treatment should be individualized based on drug susceptibility, clinical and microbiological responses, and with close consultation with experienced specialists **(AIII)**.

Other Considerations in TB Management

- Adjunctive corticosteroid improves survival for patients with HIV-related TB involving the CNS and pericardium **(AI)**.
- Dexamethasone has been used for CNS disease with the following dosing schedule: 0.3–0.4 mg/kg/day for 2–4 weeks, then taper 0.1 mg/kg per week until 0.1 mg/kg, then 4 mg per day and taper by 1 mg/week; total duration of approximately 12 weeks.
- Prednisone or prednisolone may be used in pericardial disease (e.g. 60 mg PO daily and taper by 10 mg per day weekly; total duration approximately 6 weeks)
- Despite the potential of drug-drug interactions, a rifamycin remains the most potent TB drug and should remain as part of the TB regimen unless there is rifamycin-resistant isolate or the patient has a severe adverse effect that is likely to be due to the rifamycin (please refer to the table below and to Table 5 for dosing recommendations involving concomitant use of RIF or RFB and different antiretroviral drugs).
- If NVP is to be added to a patient who is receiving RIF, the lead-in dose for nevirapine should be omitted.
- RFB is a less potent CYP 3A4 inducer than RIF and is preferred in patients receiving HIV PIs **(BIII)**.
- RPT administered once weekly can result in development of resistance in HIV-infected patients and is not recommended for patients with TB disease **(AI)**.
- Paradoxical reaction that is not severe may be treated symptomatically **(CIII)**.
- For moderately severe paradoxical reaction, may consider use of corticosteroid, and taper over 4 weeks (or longer) based on clinical symptoms **(BIII)**.

Examples of Prednisone Dosing Strategies

- In patients on a RIF-based regimen: prednisone 1.5 mg/kg/day x 2 weeks, then 0.75 mg/kg x 2 weeks
- In patients on a RFB + boosted PI based regimen: prednisone 1.0 mg/kg/day x 2 weeks, then 0.5 mg/kg/day x 2 weeks
- A more gradual tapering schedule over a few months may be necessary in some patients.

[a] Screening tests for LTBI include TST or IGRA; please see text for details regarding these tests.

Key to Abbreviations: ART = antiretroviral therapy; ARV = antiretroviral; BIW = twice weekly; CNS = central nervous system; DOT = directly observed therapy; EMB = ethambutol; INH=isoniazid; LTBI = latent tuberculosis infection; NVP = nevirapine; PI = protease inhibitor; PO = oral; PZA = pyrazinamide; RFB = rifabutin; RIF = rifampin; RPT = rifapentine; TB = tuberculosis; TIW = thrice weekly; TST = tuberculin skin test; IGRA = interferon-gamma release assays.

Dosing Recommendations for Anti-Tuberculosis Drugs for Treatment of Active TB

Drug	Daily	3x/week
Isoniazid	5 mg/kg (usual dose 300 mg)	15 mg/kg (usual dose 900 mg)
Rifampin **Note:** Rifampin is not recommended in patients receiving HIV PIs, ETR, RPV, or EVG/COBI/TDF/FTC	10 mg/kg (usual dose 600 mg)	10 mg/kg (usual dose 600 mg)
Rifabutin without HIV PIs, EFV, RPV or EVG/COBI/TDF/FTC	5 mg/kg (usual dose 300 mg)	5 mg/kg (usual dose 300 mg)
with HIV PIs	150 mg[a]	300 mg[a]
with EFV	450–600 mg	450–600 mg
with EVG/COBI/TDF/FTC	150 mg[b]	150 mg[b]
Pyrazinamide (weight-based dosing) 40–55 kg	1000 mg (18.2–25.0 mg/kg)	1500 mg (27.3–37.5 mg/kg)
56–75 kg	1500 mg (20.0–26.8 mg/kg)	2500 mg (33.3–44.6 mg/kg)
76-90 kg	2000 mg (22.2–26.3 mg/kg)	3000 mg (33.3–39.5 mg/kg)
>90 kg	2000 mg[c]	3000 mg[c]
Ethambutol (weight-based dosing) 40–55 kg	800 mg (14.5–20.0 mg/kg)	1200 mg (21.8–30.0 mg/kg)
56–75 kg	1200 mg (16.0–21.4 mg/kg)	2000 mg (26.7–35.7 mg/kg)
76-90 kg	1600 mg (17.8–21.1 mg/kg)	2400 mg (26.7–31.6 mg/kg)
>90 kg	1600 mg[c]	2400 mg[c]

[a] Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150 mg twice weekly dosing together with ritonavir-boosted PIs. May consider therapeutic drug monitoring when rifabutin is used with a ritonavir-boosted PI and adjust dose accordingly.

[b] Avoid co-administration of EVG/COBI/TDF/FTC with rifabutin, if possible. If used together, consider therapeutic drug monitoring and adjust dose accordingly.

[c] Monitor for therapeutic response and consider therapeutic drug monitoring to assure dosage adequacy in patients who weigh >90 kg.

Key to Acronyms: COBI = cobicistat; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate

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